SUPPORT FOR THE AMENDMENTS

Applicants have amended Claim 22 for clarity and to recite that the particles are ***un-agglomerated***. Support for the particles being un-agglomerated can be found, *e.g.*, on page 12, lines 3-16, of the specification, and in Figures 1-6, which clearly show that the particles are individual, un-agglomerated particles. Claims 23, 24, and 32 have been amended for clarity. Support for amended Claims 23, 24, and 32 can be found in the same claims, as previously presented.

No new matter has been added. Claims 22-29 and 31-33 remain active in the present application.

REMARKS/ARGUMENTS

Present Claims 22-29 and 31-33 relate to processes for preparing a carrier for use in the preparation of powdery mixtures for the administration by inhalation of micronized drugs, said carrier comprising a plurality of particles, said process comprising:

subjecting a first plurality of un-agglomerated particles having a median diameter of greater than 90 μm and a surface rugosity expressed as the fractal dimension of greater than 1.1 to repeated stages of wetting with a solvent and drying in a high-speed granulator,

wherein said solvent is a short-chain aliphatic alcohol or a water and alcohol mixture,

to obtain a second plurality of un-agglomerated particles having a median diameter greater than 90 μm and a surface rugosity expressed as the fractal dimension of less than or equal to 1.1.

The inventors have discovered that the presently claimed processes are particularly effective for obtaining carriers for use in the preparation of powdery mixtures for the administration by inhalation of micronized drugs. The cited references contain no disclosure

or suggestion of the presently claimed processes or the advantages afforded thereby. Accordingly, these references cannot affect the patentability of the present claims.

A technical problem underlying the present invention is to provide a process for preparing a carrier consisting of individual, not agglomerated, particles having a median diameter > 90 μm and a nearly perfectly smooth surface, *e.g.*, with a surface rugosity ≤ 1.1 upon determination of its fractal dimension (*see*, page 10, lines 25-27, and page 11, lines 9-10, of the present specification). This problem has been solved by providing a process which involves subjecting the particles to repeated stages of wetting with a solvent and drying in a high-speed mixer granulator characterized in that the wetting is carried out with a short-chain aliphatic alcohol or a water-alcohol mixture as the solvent.

Such an apparatus is designed and normally used for agglomerating solid particles and not for smoothing them individually (*see, e.g.*, page 11, lines 15-18, of the present specification). However, the present inventors have found that under certain conditions of use, it is possible to alter the surface characteristics of the carrier particles for inhalation use, without causing their agglomeration into granules or pellets (*see, e.g.*, page 12, lines 3-14, of the present specification).

The rejection of Claims 22-29 and 31-33 under 35 U.S.C. § 103(a) in view of U.S. Patent No. 5,376,386 (Ganderton et al.) in view of EP 0 786 526 (Kato et al.) is respectfully traversed. As conceded on page 3 of the Office Action, Ganderton et al. does not disclose a method of producing smooth carrier particles utilizing a high-speed granulator using an alcohol or a water-alcohol mixture as a solvent. Applicants respectfully submit that there is nothing in Kato et al. which can cure this basic deficiency.

Kato et al. discloses spherical particles made substantially of lactose having high surface smoothness with low abrasiveness, which are in the form of granules. Said granules are obtained by granulating powdered lactose (*see*, col. 3, lines 56-57). The production of the

granules of Kato et al., involves the use of ***water, an aqueous solution of lactose, or a dilute aqueous solution of a water-soluble polymer*** (see, col. 6, lines 23-30). Kato et al. is completely silent in regard to the use of a short-chain aliphatic alcohol or a water and alcohol mixture.

Thus, the process disclosed in Kato et al. differs from that which is presently claimed in at least two regards:

1. First, the process of Kato et al. does not involve the use of a solvent which is either: (a) a short chain aliphatic alcohol or (b) a water-alcohol mixture; and

2. Second, the process of Kato et al. affords granules which are agglomerates, not individual un-agglomerated particles.

Turning to the first difference, as already noted above, Ganderton et al. also does not disclose a method utilizing a high-speed granulator with a short-chain aliphatic alcohol or a water-alcohol mixture as a solvent.

Thus, neither Ganderton et al. nor Kato et al. disclose a method utilizing a high-speed granulator with a short-chain aliphatic alcohol or a water-alcohol mixture as a solvent. Accordingly, no matter how these references are combined, the resulting combination does not include the use of a high-speed granulator with a short-chain aliphatic alcohol or a water-alcohol mixture as a solvent.

For this reason, these references, even in combination, cannot create a *prima facie* case of obviousness against the present claims.

Turning to the second difference, it is the surprising discovery of the present inventors that the presently claimed method affords un-agglomerated particles. There is nothing in either of the cited references which would suggest this surprising result.

On page 5, the position is taken that the term granule reads on individual (i.e. un-agglomerated) particles. However, Applicants submit that to the extent this assertion is relevant, it is incorrect.

First, in the context of the present application, the only meanings of the terms "granule" and "granulating" which are relevant are how those terms are used in Kato et al. In this case, it is clear that Kato et al. uses the term "granule" to describe an agglomerated product and the term "granulating" to a process of agglomerating a powder to a larger product. These conclusions are unavoidable after a close inspection of Kato et al.

In particular, the Examiner's attention is directed toward the examples of Kato et al. As can be seen, the particle size of the final product of Kato et al. is larger than that of the starting powder. For example, in Example 1 of Kato et al., the particle size of the starting material core crystalline lactose was 212-425 μm and that of the powdered lactose was 12.5 μm, while that of the product after granulation was 500-710 μm.

Thus, Kato et al. also states that:

> Powdered lactose used according to the invention is lactose powder of pass through a sieve of 75 μm, and preferably it is of smaller than 1/10 the average particle size of the crystalline lactose or lactose granules serving as the nuclei. Powdered lactose of smaller particle size is preferred, and fine crystalline lactose may also be used.
>
> The crystalline lactose serving as the nuclei according to the invention is crystalline lactose with a particle size of at least pass through a sieve of 75 micron, and crystalline lactose with a particle size of pass through a sieve of 300 micron, no pass through a sieve of 150 micron is particularly preferred.

Kato et al., col. 3, lines 41-54.

Moreover, Kato et al. explicitly describes the structure of the final product as one in which the "powder lactose had adhered and fixed around the outside" (*see*, col. 7, lines 35-41).

Further, in Claim 1, Kato et al. explicitly describes the product as existing in "aggregate form."

Thus, Kato et al. explicitly describes its product as one in which powder particles are adhered to the outside of nuclei particles.

In this respect, it is instructive to compare the electron micrographs from the present application with those provided in Kato et al. From such a comparison, it can be *de visu* appreciated that the particles obtained by the presently claimed processes are completely different from the agglomerated granules of Kato et al.

An image of particles produced according to the presently claimed process is reported in Figure 1(d). As can be readily seen, they are in the form of individual, and hence not agglomerated. It can also be appreciated that they display a smoothed surface in comparison to the particles which have not been subjected to the process of the invention (*see, e.g.*, Figure 1(a)).

In contrast, the electron micrographs of the granules of Kato et al., shown in Figures 3, 4 and 5 of that reference, clearly show that the particles have a much larger diameter (*see*, scale at the bottom of the figures). These electron micrographs clearly show that the granules of Kato et al. are not individual un-agglomerated particles.

Therefore the particles obtained by the presently claimed processes are completely different from the granules of Kato et al. Specifically, Kato et al. discloses the preparation of particles in the form of ***granules***, *i.e.* particles which are obtained from ***agglomeration by granulation*** of smaller particles, said granules being suitable for controlling the release of drugs and improving the resistance to disintegration of sustained-release formulations.

Since the aim of the present invention is to make ***individual (not agglomerated)*** particles with a smooth surface as a carrier for inhalation of micronized drugs and not to make ***granules***, it is respectfully submitted that the teachings of Kato et al. are not relevant to

the presently claimed process, and hence the skilled person would not combine the teachings of Ganderton et al. and Kato et al.

For all of these reasons, the rejection is improper and should be withdrawn.

In specific regard to present Claim 23, Applicants submit that there is nothing in either of the cited references, even in combination which would suggest using the presently claimed processes to obtain particles having a median diameter of from 90 to 150 micron. In particular, as noted above, Kato et al. is concerned with making much larger particles.

Accordingly, Claim 23 is certainly patentable.

The rejection of Claims 22-29 and 32-33 under the judicially-created doctrine of obviousness-type double patenting in view of Claims 1-12 of U.S. Patent No. 6,780,508 ("the '508 patent") is respectfully traversed. As noted above, present independent Claim 22 recites the use of "a short-chain aliphatic alcohol or a water and alcohol mixture." Applicants respectfully submit that there is nothing in the claims of the '508 patent which would suggest such a method. On page, 7 of the Office Action, the Examiner refers to the disclosure of the '508 patent to augment the claims of the '508 patent. However, this is improper. Simply put, there is nothing in the claims of the '508 patent which would suggest the presently claimed processes.

Accordingly, the rejection is improper and should be withdrawn.

Applicants submit that the application is now in condition for allowance, and early notification of such action is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
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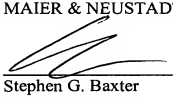

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